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Original Article

Changing thresholds and incidence of antibiotic treatment of cystic fibrosis pulmonary exacerbations, 1995–2005

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Abstract

Background: Increased chronic therapy use and improved cystic fibrosis (CF) patient health should be accompanied by reduced pulmonary exacerbation-associated antibiotic treatment incidence.
Methods: Treatment incidence rates and associated sign/symptom scores from 1995–2005 were studied in Epidemiologic Study of CF patients by route (±IV) and age (<6, 6–12, 13–17, ≥18 years).
Results: Overall treatment incidence rate fell 0.0165 events/patient-year/year ($P=.006$); IV incidence fell 0.0179 ($P<.001$). Non-IV incidence *increased* in children ≤12 years ($P\leq.002$) while significantly decreasing in older patients. Mean IV ($P=.046$) and non-IV ($P=.004$) treatment-associated clinical scores decreased in children <6 years. Non-IV (but not IV) clinical scores decreased in older patients.
Conclusions: IV incidence fell for all ages from 1995–2005; non-IV incidence *increased* in patients ≤12 years and fell in others. Average clinical treatment thresholds fell in children <6 years; IV thresholds were unchanged in older patients; non-IV thresholds fell for patients ≥13 years. Decreases in treatment incidence were likely partially offset by lower treatment thresholds.

Keywords: Cystic fibrosis; Pulmonary exacerbation; Epidemiology; Treatment thresholds

1. Introduction

Pulmonary exacerbations (PEx) present unique challenges to persons with cystic fibrosis (CF), their caregivers, CF drug developers, and regulators. Although PEx are resource-intensive events [1] that reduce patient quality of life [2–4], are associated with morbidity [5], contribute to lung disease progression [6], and are associated with reduced survival [7–9], a consensus prospective definition of PEx remains elusive [5]. In the absence of an accepted prospective definition, CF epidemiologists and drug developers have employed a surrogate indicator of PEx: antibiotic treatment in response to acute changes in respiratory signs and symptoms. Although this pragmatic approach has allowed estimation of the incidence of and risk factors associated with antibiotic treatment for PEx [10,11] and treatment-associated outcomes [6,12], it has important shortcomings. Clinician thresholds for prescribing antibiotic treatment may differ [13], possibly as a result of experience and management style. Thus, a given patient history and clinical presentation may precipitate antibiotic treatment (and thus be considered a PEx) in one setting but not in another.

Despite variability associated with antibiotic treatment as a surrogate measure for PEx, investigators have demonstrated

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that chronic CF treatment with mucus-active agents [14,15], surface liquid hydrators [16,17], inhaled antibiotics [18–20], macrolides [21–23], and *CFTR* potentiators [24,25] significantly increase the time to and/or reduce the need for antibiotic treatment of respiratory symptoms associated with PEx. As the benefits of these therapies have been characterized, their use has increased [26] and become incorporated into "standards" of chronic CF respiratory care [27,28]. During the same period, the overall health of the CF population has increased [29], which in turn would be expected to be reflected in a noticeable reduction in the incidence of antibiotic treatment for PEx over time. Interestingly, there has been little evidence that antibiotic treatment incidence for PEx has appreciably changed over past decades [30], suggesting either that chronic CF therapies and improved overall health are less effective at reducing PEx than may have been previously believed, or that thresholds at which CF clinicians intervene to treat increased respiratory signs and symptoms have evolved over time, or both.

We have studied the demographics of PEx-associated treatments in the Epidemiologic Study of Cystic Fibrosis (ESCF) [31] from 1995 through 2005. PEx-associated antibiotic treatments stratified by route of administration (intravenous [IV] versus non-IV) were analyzed to characterize year-to-year changes in incidence rates during the period. When available, acute changes in clinical signs and symptoms of age-specific variables shown to be associated with PEx treatment [32] were tabulated to estimate clinical thresholds for antibiotic intervention over the period.

2. Methods

Patient encounters recorded in ESCF in which health professionals administered antibiotics and reported that these treatments were specifically intended for the management of a physician-identified PEx were studied. Antibiotic treatments that were not administered for the management of what the treating physician considered to be a PEx were excluded. Documentation of patient age, sex, and date of ESCF enrollment was required for study inclusion. Antibiotic treatment events were stratified as being either IV treatments (where IV antibiotics were administered at some point during treatment) or non-IV treatments (where no IV antibiotics were administered over the course of treatment). Physician-identified PEx (hereafter referred to simply as PEx) treatment events were also stratified by the calendar year in which they occurred (1995–2005) and the patient's age group on December 31st of that year (<6, 6–12, 13–17, and ≥18 years of age). The incidence rates of antibiotic treatment events associated with PEx in each year and age subgroup were calculated by dividing the number of observed PEx treatment events by the total number of patient-years followed in ESCF for each age subgroup each year.

When data were available, scores ranging from 0 to 4 representing changes in clinical signs and symptoms associated with PEx treatment encounters were determined using a modification of the system originally described by Rabin et al. [32] (Table 1). For each age group, four age-specific clinical parameters previously shown to be associated with PEx antibiotic treatment [32] were assessed at the antibiotic treatment encounter and at the patient's most recent previous stable encounter. A modified Rabin score of 0 indicated no changes in clinical parameters from the previous stable encounter, whereas a score of 4 indicated a worsening in all four age group-specific parameters from the previous encounter. Description of raw parameter values and algorithms for identifying change from previous stable encounters to PEx encounters are shown in Table 1. Average

Table 1
Algorithm for scoring changes in clinical characteristics between most recent previous (stable) encounter and pulmonary exacerbations (PEx) antibiotic treatment encounter.

Clinical characteristic	Raw value at encounters	Condition indicating change from stable to PEx encounters	Relevant age groups, years [a]			
			<6	6–12	13–17	18+
New crackles	0=no 1=yes	[PEx]−[stable]=1	X	X	X	X
Increased cough	0=none 1=occasionally 2=daily	[PEx]−[stable]>0	X	X	X	X
Increased sputum	0=none 1=occasionally 2=daily	[PEx]−[stable]>0	X			
WFA decline	0–100 (percentile)	([PEx]−[stable])/[stable] ≤ −0.45	X			
FEV_1 decline	10–150 (% predicted)	([PEx]−[stable])/[Stable] ≤ −0.15		X	X	X
New *P. aeruginosa*	0=negative 1=positive	[PEx] [b] − [stable] [c] =1		X		
Presence of hemoptysis	0=none 1=scant 2=sub massive 3=massive	[PEx]>0			X	X

[a] Age group(s) for which individual scoring algorithms were applied, based on Rabin et al. [31]. Four measures of clinical change are applied to each age group (noted by "X"), producing a modified Rabin score ranging from 0 to 4 changes from immediate stable encounter.
[b] Any culture result within 2 weeks prior to and including PEx encounter.
[c] All culture results in the year (excluding the last 2 weeks) prior to PEx encounter.

modified Rabin scores associated with PEx antibiotic treatment were calculated for age and treatment type subgroups for each calendar year.

Changes in the incidence of antibiotic treatment for PEx (as treatment events per patient-year) and mean modified Rabin scores associated with treatment over the study period were assessed by simple linear regression. Proportions of year-to-year variance in treatment incidence and mean modified Rabin scores explained by time (R^2) and associated P values for nonzero regression slopes were calculated. All analyses were conducted using SAS 9.2 (SAS Institute, Inc., Cary, NC).

3. Results

A total of 209,056 PEx-associated antibiotic treatments were recorded over 186,273 ESCF patient-years studied between 1995 and 2005, resulting in an average incidence of 1.12 antibiotic treatment events per patient-year. Of these, 102,689 (49.1%) were non-IV antibiotic treatments and 106,367 (50.9%) were IV treatments, corresponding to treatment incidences of 0.55/patient-year and 0.57/patient-year, respectively. Overall antibiotic treatment incidence decreased over the study period (slope = −0.0165 events per patient-year/year, $R^2 = 0.58$; $P = .006$), with this change largely accounted for by a reduction in IV (slope = −0.0179, $R^2 = 0.77$; $P < .001$) but not in non-IV treatment incidence (slope = +0.0014, $R^2 = 0.03$; $P = .710$).

Marked differences by age group were observed in antibiotic treatment incidence over the study period (Fig. 1). Initially, antibiotic treatment incidence roughly correlated with age group, with adult treatment incidence approximately 3 times higher than that of patients less than 6 years of age and intermediate treatment incidence for patients of intermediate age. Over the study period, adult treatment incidence steadily fell (slope = −0.0628, $R^2 = 0.86$, $P < .001$), as did treatment incidence in 13- to 17-year-olds (slope = −0.0348, $R^2 = 0.75$, $P < .001$), while treatment incidence in children less than 6 increased (slope = +0.0290, $R^2 = 0.62$, $P = .004$) and was essentially unchanged in 6- to 12-year-olds (slope = +0.0049, $R^2 = 0.16$, $P = .220$) (Fig. 1A). By the end of the observation period, overall antibiotic treatment incidence was similar across age groups.

Changes over time in antibiotic treatment incidence differed by antibiotic delivery route (IV versus non-IV) (Fig. 1B and C). IV antibiotic treatment incidence consistently fell for all age groups across the period (Fig. 1C and Table 2), while non-IV treatment incidence increased in younger patients and fell in older patients (Fig. 1B and Table 2). Although the rates at which treatment incidence was observed to change over the period were not large, all were statistically and significantly different from zero (Table 2).

Only 14.5% (30,357) of the 209,056 antibiotic treatment events studied had sufficient accompanying data to be evaluable by the modified Rabin clinical scoring algorithm (Table 1). Events occurring in children less than 6 years old were most likely to be evaluable, with an average of 27.0% of events being evaluable per year, while events in 6–12 year olds were least likely to be evaluable, with an average of 10.6% evaluable events per year. With two exceptions (events in 1995 for patients 6 to 12 years of age and in 1997 for patients 13 to 17 years of age),

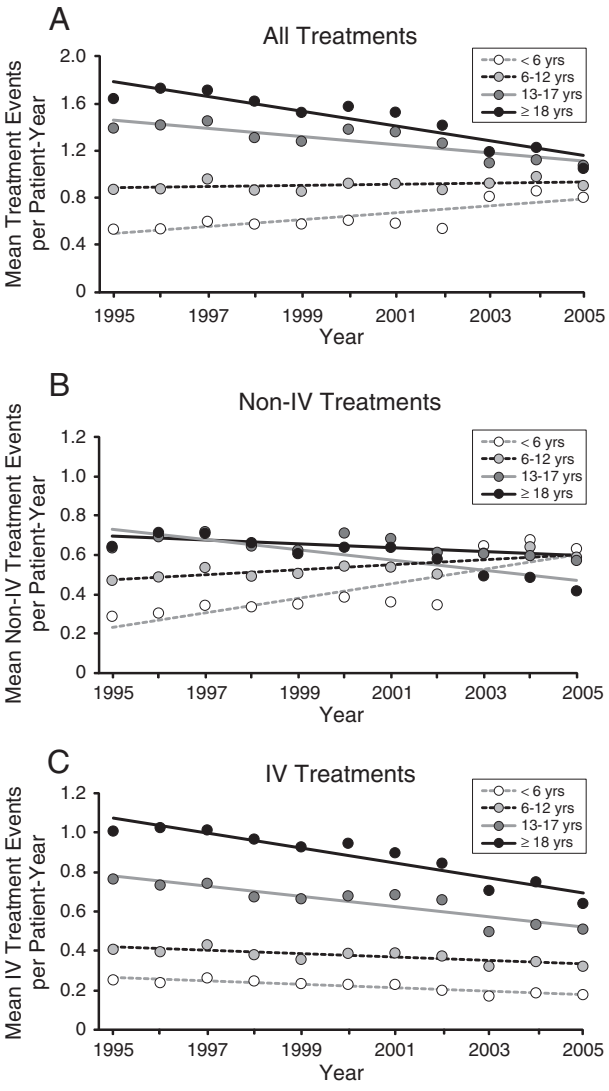

Fig. 1. Average annual incidence of antibiotic treatment events associated with pulmonary exacerbations from 1995–2005 by administration route and age group. Panel A, average incidence of all antibiotic treatment events. Panel B, incidence of antibiotic treatment events not including IV antibiotics. Panel C, incidence of antibiotic treatment events in which IV antibiotics were included. Open circles with gray dashed lines, patients less than 6 years of age. Light gray circles with black dashed lines, patients 6 to 12 years of age. Dark gray circles with solid gray line, patients 13 to 17 years of age. Black circles with black lines, patients 18 years of age and older. Note that vertical axes for Panels B and C differ from that of Panel A.

mean modified Rabin scores were always higher for IV compared to non-IV interventions each year in every age group. This difference at the population level is reflected in mean differences between IV and non-IV scores across the study period for each age group (Fig. 2A). Although associated clinical scores were higher on average for patients treated with IV antibiotics than for those not treated with IV antibiotics, clinical scores were not predictive of antibiotic administration route, as 71.0% of patients treated with IV antibiotics had associated Rabin scores of 0 or 1, compared with 76.6% of patients treated with non-IV antibiotics (Fig. 2B). Similarly, 4.6% of patients treated with non-IV antibiotics had associated clinical scores of 3 or 4, compared with 7.3% of those whose treatment included IV antibiotics.

Table 2
Changes in pulmonary exacerbations antibiotic treatment event incidence by age group and route of administration, 1995–2005.

	Slope, events/patient-year/year (SE [a])	R^2	P value [b]
Non-IV antibiotic treatment events			
<6	0.0376 (0.0080)	0.71	.001
6–12	0.0133 (0.0032)	0.67	.002
13–17	−0.0094 (0.0038)	0.41	.034
≥18	−0.0256 (0.0044)	0.79	<.001
IV antibiotic treatment events			
<6	−0.0086 (0.0013)	0.83	<.001
6–12	−0.0084 (0.0020)	0.67	.002
13–17	−0.0253 (0.0040)	0.82	<.001
≥18	−0.0372 (0.0044)	0.89	<.001

[a] Standard error.
[b] Test for nonzero slope.

Table 3
Changes in mean modified Rabin clinical scores associated with evaluable antibiotic treatment events by age group and route of administration, 1995–2005.

	Slope, Rabin score/year (SE [a])	R^2	P value [b]
Non-IV antibiotic treatment events			
<6	−0.0207 (0.0054)	0.62	.004
6–12	−0.0129 (0.0058)	0.35	.054
13–17	−0.0111 (0.0036)	0.51	.014
≥18	−0.0092 (0.0018)	0.75	<.001
IV antibiotic treatment events			
<6	−0.0268 (0.0116)	0.37	.046
6–12	0.0050 (0.0090)	0.03	.590
13–17	−0.0029 (0.0087)	0.01	.740
≥18	−0.0022 (0.0034)	0.05	.530

[a] Standard error.
[b] Test for nonzero slope.

Over the observation period, mean annual Rabin scores associated with both non-IV antibiotic treatments and IV treatments decreased significantly (P=.004 and P=.046, respectively) for children less than 6 years of age (Table 3). Reduced mean annual clinical scores for non-IV treatments were also observed in older patients across the observation period, reaching statistical significance in 13- to 17-year-olds (P=.014) and adults (P<.001), but not children 6 to 12 years of age (P=.054) (Table 3). In contrast, no consistent trends were observed in clinical score changes associated with IV antibiotic treatments in patients 6 years of age and older (Fig. 3).

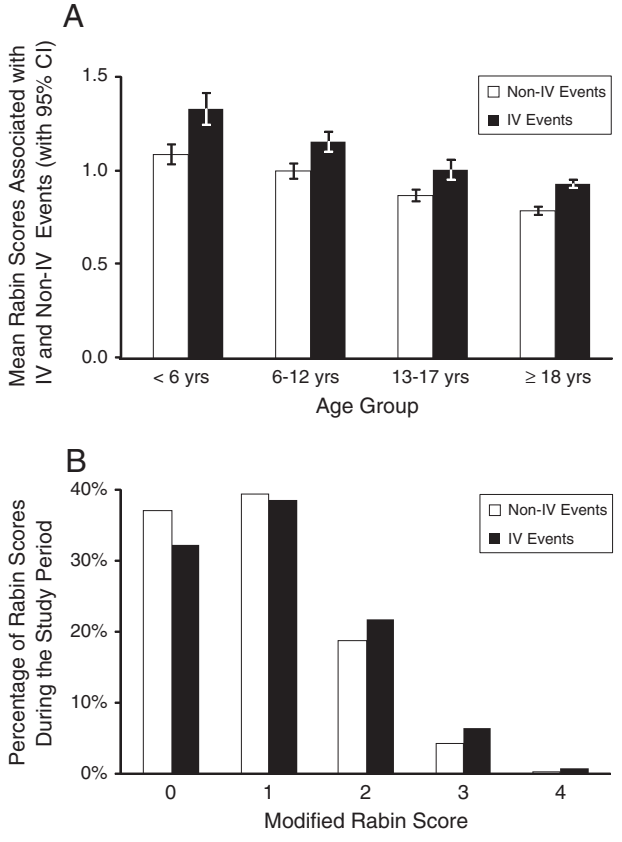

Fig. 2. Distributions of modified Rabin scores and mean annual differences in mean modified Rabin scores for evaluable IV and non-IV treatment events by age group. Clear bars, antibiotic treatments not including IV antibiotics. Black bars, treatments including IV antibiotics. Panel A, mean modified Rabin clinical scores associated with pulmonary exacerbation treatment events between 1995 and 2005 by route of administration and age group. Possible scores range from 0 to 4. Bars show 95% confidence intervals for means. Panel B, distributions of treatment-associated modified Rabin scores between 1995 and 2005 by route of administration.

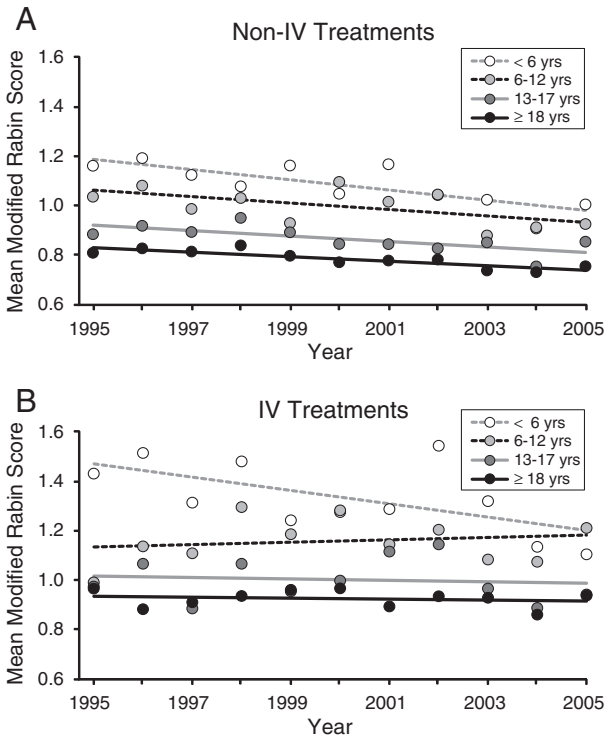

Fig. 3. Average modified Rabin clinical scores associated with pulmonary exacerbations from 1995–2005 by antibiotic administration route and age group. Panel A, modified Rabin scores associated with antibiotic treatment events not including IV antibiotics. Panel B, modified Rabin scores associated with antibiotic treatment events in which IV antibiotics were included. Open circles with gray dashed lines, patients less than 6 years of age. Light gray circles with black dashed lines, patients 6 to 12 years of age. Dark gray circles with solid gray line, patients 13 to 17 years of age. Black circles with black lines, patients 18 years of age and older.

4. Discussion

Over recent decades, the intensity with which CF patients have been treated with chronic respiratory therapies shown to reduce risk of antibiotic treatment for PEx has markedly increased [26]. Over this same period, mean and median population measures for factors associated with antibiotic treatment for PEx, including pulmonary function and weight-for-age and respiratory signs and symptoms [5,11], have steadily improved [29,30]. A logical conclusion from these two observations would be that the incidence of antibiotic treatment for PEx in the population should have decreased during the period. However, such a conclusion includes an assumption that clinician behavior regarding PEx diagnosis and antibiotic intervention have not changed over time.

Our results suggest that there had, in fact, been a detectable reduction in the incidence of treatment with IV antibiotics for PEx between 1995 and 2005 across the CF population, but that this reduction was more nuanced than might have been expected, being more pronounced in older patients than in younger ones (Fig. 1C and Table 2). Further, the incidence of antibiotic treatments that did not include IV antibiotics actually *increased* significantly in CF patients less than 12 years of age while decreasing significantly in older patients over the period (Table 2). This distinction in antibiotic treatment incidence change over the period between younger and older patients appears to have been driven at least in part by changing thresholds for intervention in younger patients, where significantly fewer clinical symptoms (on average) were associated with interventions in children less than 6 years of age over time (Table 3). Although observed changes in IV antibiotic treatment incidence coincided with an increased intensity of chronic therapy use during the period [26], we have not demonstrated a causal relationship between the two.

These data highlight inherent challenges in using antibiotic treatment as a surrogate for clinical diagnosis of PEx. Although such an approach may be valid in controlled randomized trials of relatively short duration, clinician attitudes and practice patterns have the potential to change (and in this case apparently did change) over longer periods of observation. These data also highlight the challenges in using retrospective analyses to "score" clinical symptoms associated with PEx. The original Rabin study identified clinical presentations most commonly associated with PEx treatment: a clinical encounter in which a patient presented with a Rabin score of 3 or 4 was highly likely to result in antibiotic treatment for PEx [32]. However, Rabin et al. never suggested that the converse was true: that antibiotic treatment for PEx was highly likely to be associated with a Rabin score of 3 or 4. In fact, a large percentage of PEx resulting in antibiotic treatments were associated with Rabin scores of 0 or 1, as we also observed in this study. This distinction reflects the difficulty in reducing the constellation of signs and symptoms that may lead to a clinical diagnosis of PEx [5] to a manageable few for the purposes of development of a clinical score.

There is a real evidence of a significant reduction in the antibiotic treatment incidence for PEx between 1995 and 2005. However, clinical practice patterns with respect to pulmonary sign and symptom thresholds for antibiotic intervention, particularly in the youngest CF patients, have evolved in parallel over the time period, appearing to partially offset what might have been an even greater reduction in treatment incidence. These results suggest that epidemiologists and clinical trial designers should exercise caution when using historical data or data averaged over extended periods to draw conclusions with respect to antibiotic treatments for PEx.

Disclosure

This study is sponsored by Genentech, Inc. Donald VanDevanter, Wayne Morgan, and Michael Konstan have received honoraria from Genentech for serving as members of the North American Scientific Advisory Group for the Epidemiologic Study of Cystic Fibrosis (ESCF) and have served as consultants to Genentech. No compensation was provided to these authors in exchange for production of this manuscript. Eric Elkin and David Pasta are employees of ICON Late Phase & Outcomes Research, which was paid by Genentech for providing analytical services for this study. The decision to submit the manuscript was made by the authors and approved by Genentech.

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References

[1] Ouyang L, Grosse SD, Amendah DD, Schechter MS. Healthcare expenditures for privately insured people with cystic fibrosis. Pediatr Pulmonol 2009;44:989–96.
[2] Orenstein DM, Pattishall EN, Nixon PA, Ross EA, Kaplan RM. Quality of well-being before and after antibiotic treatment of pulmonary exacerbation in patients with cystic fibrosis. Chest 1990;98:1081–4.
[3] Bradley J, McAlister O, Elborn S. Pulmonary function, inflammation, exercise capacity and quality of life in cystic fibrosis. Eur Respir J 2001;17: 712–5.
[4] Britto MT, Kotagal UR, Hornung RW, Atherton HD, Tsevat J, Wilmott RW. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. Chest 2002;121:64–72.
[5] Ferkol T, Rosenfeld M, Milla CE. Cystic fibrosis pulmonary exacerbations. J Pediatr 2006;148:259–64.
[6] Sanders DB, Hoffman LR, Emerson J, et al. Return of FEV(1) after pulmonary exacerbation in children with cystic fibrosis. Pediatr Pulmonol 2010;45:127–34.
[7] Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. Am J Epidemiol 2001;153:345–52.
[8] Mayer-Hamblett N, Rosenfeld M, Emerson J, Goss CH, Aitken ML. Developing cystic fibrosis lung transplant referral criteria using predictors of 2-year mortality. Am J Respir Crit Care Med 2002;166:1550–5.
[9] Emerson J, Rosenfeld M, McNamara S, Ramsey B, Gibson RL. *Pseudomonas aeruginosa* and other predictors of mortality and morbidity in young children with cystic fibrosis. Pediatr Pulmonol 2002;34:91–100.
[10] Goss CH, Burns JL. Exacerbations in cystic fibrosis. 1: epidemiology and pathogenesis. Thorax 2007;62:360–7.
[11] VanDevanter DR, Yegin A, Morgan WJ, Millar SJ, Pasta DJ, Konstan MW. Design and powering of cystic fibrosis clinical trials using pulmonary exacerbation as an efficacy endpoint. J Cyst Fibros 2011;10:453–9.
[12] Wagener JS, VanDevanter DR, Regelmann W, et al. Oral, inhaled, and intravenous antibiotic choice for treating pulmonary exacerbations in cystic

fibrosis. Pediatr Pulmonol Aug 8 2012, http://dx.doi.org/10.1002/ppul.22652 [Epub ahead of print].
[13] Kraynack NC, Gothard MD, Falletta LM, McBride JT. Approach to treating cystic fibrosis pulmonary exacerbations varies widely across US CF care centers. Pediatr Pulmonol 2011;46:870–81.
[14] Fuchs HJ, Borowitz DS, Christiansen DH, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. N Engl J Med 1994;331:637–42.
[15] Quan JM, Tiddens HA, Sy JP, et al. A two-year randomized, placebo controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. J Pediatr 2001;139:813–20.
[16] Elkins MR, Robinson M, Rose BR, et al. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. N Engl J Med 2006;354:229–40.
[17] Jaques A, Daviskas E, Turton JA, et al. Inhaled mannitol improves lung function in cystic fibrosis. Chest 2008;133:1388–96.
[18] Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. N Engl J Med 1999;340:23–30.
[19] Murphy TD, Anbar RD, Lester LA, Nasr SZ, Nickerson B, VanDevanter DR, et al. Treatment with tobramycin solution for inhalation reduces hospitalizations in young CF subjects with mild lung disease. Pediatr Pulmonol 2004;38:314–20.
[20] McCoy KS, Quittner AL, Oermann CM, Gibson RL, Retsch-Bogart GZ, Montgomery AB. Inhaled aztreonam lysine for chronic airway *Pseudomonas aeruginosa* in cystic fibrosis. Am J Respir Crit Care Med 2008;178:921–8.
[21] Equi A, Balfour-Lynn IM, Bush A, Rosenthal M. Long term azithromycin in children with cystic fibrosis: a randomised, placebo-controlled crossover trial. Lancet 2002;360:978–84.
[22] Wolter J, Seeney S, Bell S, Bowler S, Masel P, McCormack J. Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial. Thorax 2002;57:212–6.
[23] Saiman L, Marshall BC, Mayer-Hamblett N, et al. Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*: a randomized controlled trial. JAMA 2003;290:1749–56.
[24] Accurso FJ, Rowe SM, Clancy JP, et al. Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. N Engl J Med 2010;363:1991–2003.
[25] Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011;365:1663–72.
[26] Konstan MW, VanDevanter DR, Rasouliyan L, et al. Trends in the use of routine therapies in cystic fibrosis: 1995–2005. Pediatr Pulmonol 2010;45:1167–72.
[27] Flume PA, Mogayzel Jr PJ, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. Am J Respir Crit Care Med 2009;180:802–8.
[28] Heijerman H, Westerman E, Conway S, Touw D, Döring G, consensus working group. Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: a European consensus. J Cyst Fibros 2009;8:295–315.
[29] VanDevanter DR, Rasouliyan LH, Murphy TM, et al. Trends in the clinical characteristics of the U.S. cystic fibrosis patient population from 1995 to 2005. Pediatr Pulmonol 2008;43:739–44.
[30] Cystic Fibrosis Foundation. Patient registry 2010. Annual data report to the center directors. Bethesda MD: Cystic Fibrosis Foundation; 2011.
[31] Morgan WJ, Butler SM, Johnson CA, et al. Epidemiologic study of cystic fibrosis: design and implementation of a prospective, multicenter, observational study of patients with cystic fibrosis in the U.S. and Canada. Pediatr Pulmonol 1999;28:231–41.
[32] Rabin HR, Butler SM, Wohl ME, et al. Pulmonary exacerbations in cystic fibrosis. Pediatr Pulmonol 2004;37:400–6.